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Running head: Allopurinol and hip fracture

Abstract

Background:

Allopurinol reduces oxidative stress and interacts with purinergic signalling systems important in bone metabolism and muscle function. We assessed whether allopurinol use was associated with a reduced incidence of hip fracture in older people.

Methods:

Analysis of prospective, routinely-collected health and social care data on patients undergoing health and social work assessment in a single geographical area over a 12 year period. Exposure to allopurinol was derived from linked community prescribing data, hospitalisation for hip fracture and comorbid disease was derived from linked hospitalisation data. Fine and Gray modelling was used to model time to hip fracture accounting for the competing risk of death, incorporating previous use of allopurinol, cumulative exposure to allopurinol as a time dependent variable, and covariate adjustments.

Results:

17308 patients were alive at the time of first social work assessment without previous hip fracture; the mean age was 73 years. 10171 (59%) were female, and 1155 (8%) had at least one exposure to allopurinol. 618 (3.6%) sustained a hip fracture, and 4226 (24%) died during a mean follow up of 7.2 years. In fully-adjusted analyses, each year of allopurinol exposure conferred a hazard ratio of 1.01 (95% CI 0.99, 1.02; p=0.37) for hip fracture and 1.00 (0.99, 1.01; p=0.47) for death. Previous use of allopurinol conferred a hazard ratio of 0.76 (0.45, 1.26; p=0.28) for hip fracture and 1.13 (0.99, 1.29; p=0.07) for death.

Conclusion:

Greater cumulative use of allopurinol was not associated with a reduced risk of hip fracture or death in this cohort.

Keywords: Gout, fracture, older, allopurinol, risk factor

Introduction

Falls and fragility fractures remain a major global healthcare issue for older people. Although a range of effective therapies for osteoporosis and falls have been available for several years, admissions to hospital for osteoporosis-related fractures remain high, with major healthcare costs [1]. Effective prevention of fragility fractures requires that risk factors for both falling (e.g. impaired balance, sarcopenia) and impaired bone structure (osteoporosis/osteopenia) are addressed [2]; few interventions currently available address both of these aspects of fracture prevention.

Recent advances in bone and muscle biology have revealed two biological pathways of relevance to the current investigation. Firstly, purinergic signalling has been shown to play an important role in bone biology [3], and also has a potential role in muscle biology [4]. Multiple types of puringeric receptor are found on both myocytes [5], osteoblasts and osteoclasts; signalling via the actions of ATP on purinergic receptors can enhance osteoclast function and inhibit matrix mineralisation by osteoblasts [4]. Other agents with purinergic effects (e.g. clopidogrel) have been shown to have important biological effects on osteoblast function, again reducing mineralisation [6]. It is therefore possible that other agents active at selected purinergic receptor subtypes might have the ability to inhibit the deleterious effects of ATP on bone mineralisation. Secondly, oxidative stress has been shown to have a key role in both impaired muscle function (a factor in falls in older people) [7] via reduction of mitochondrial efficiency, and in bone biology. Reactive oxygen species such as hydrogen peroxide and the superoxide anion inhibit both osteoblast differentiation and expression of genes required for new bone formation. [8, 8a-8c]. Given the deleterious effects of oxidative stress on both muscle

and bone biology, agents that inhibit the formation of reactive oxygen species might have benefit in improving muscle function and bone formation, hence reducing the risk of fracture.

Allopurinol is a prodrug commonly used to treat gout, via its effects on inhibition of xanthine oxidase. However, xanthine oxidase is also a powerful generator of reactive oxygen species; allopurinol treatment has been shown to dramatically reduce oxidative stress in other organ systems, particularly the cardiovascular system [9]. In addition, allopurinol, as a purine analog, may have direct actions at purinergic receptors, and by inhibiting breakdown of purinergic nucleotides (e.g. ADP) by xanthine oxidase, it may also indirectly modulate the impact of ADP on purinergic signalling systems. However, any relationship between allopurinol use and fracture is likely to be complex; recent observational data suggest that elevated circulating urate levels are associated with higher bone mineral density and lower fracture risk [10-14], possibly due to antioxidant effects of urate itself. Hence analyses of the effect of allopurinol on fracture risk need to try and separate the effect of gout (a consequence of hyperuricemia) from gout treatment (allopurinol).

We have previously shown that allopurinol use is associated with greater improvements in functional status in older patients undergoing inpatient rehabilitation [15]. The aim of this analysis was to explore whether, given the biological actions of allopurinol outlined above, allopurinol use is associated with lower rates of fragility fractures and injurious falls in a group of older patients referred to social services.

Methods

Study population

We studied a cohort of older patients referred to social services over a 12 year period (January 2000 to December 2011) in Dundee, Scotland. Details of the linked datasets used in this analysis have been published previously [16,17]. The Dundee social work database contains routinely collected data on clients including details of care packages provided or commissioned by social work. We have linked data on those clients aged 65 and over with data held by the University of Dundee Health Informatics Centre (HIC) on a range of other routinely collected healthcare data. Information on community prescribing, biochemistry and haematology results, plus hospitalization data and diagnoses (Scottish Morbidity Register 01) coded using ICD-10 codes were accessible. Data from the Scottish Government Records Office, which records all deaths registered within Scotland, was held by HIC and was used as a source for date of death. For this analysis, data from the first assessment by Dundee Social Work were used. Analyses were confined to those aged 65 and over; those with a hip fracture sustained prior to the date of discharge from rehabilitation were excluded because their very high rate of death, further fracture and dependency could lead to an altered relationship between prescribing patterns and outcomes. Use of this dataset allowed us to study a group of older people at risk of dependency (hence their referral for social work assessment) and therefore at higher risk of adverse events; the presence of data on provision of care packages allowed use of this as a proxy measure of functional impairment – a powerful indicator of future adverse events including falls, fractures and death – to be included in the analyses.

Allopurinol exposure

Allopurinol use was obtained from prescription records of patients held within HIC data for community based prescriptions. The number of days of allopurinol prescription was used as a

measurement of exposure. Two indices of exposure were calculated: a) the cumulative number of years of allopurinol dispensed after discharge from rehabilitation, b) a flag denoting those who had been dispensed any prescription for allopurinol prior to the date of social work assessment. Allopurinol is prescribed for gout, which is itself associated with cardiovascular disease [18] and hence an increased rate of death and disability. Use of a 'previously exposed' variable thus allowed the effect of confounding by indication to be separated from the effect of cumulative allopurinol exposure, and separation of pre- and post-admission exposure allowed time-dependent analysis to be performed from a defined start point whilst still taking into account previous exposure.

Definition of outcome events

Data on hospitalisations for hip fractures were obtained for each patient using records held within HIC data. Relevant ICD-10 codes were identified and used to flag the date of events. ICD-10 codes for hip fracture were S72.0, S72.1, S72.2, S72.8 and S72.9. Primary and secondary diagnosis codes were included. The number of days from social services assessment to the date of first admission for which a hip fracture discharge code was present was then calculated for each patient who suffered such an event. Those who suffered a fracture prior to rehabilitation were not included in the analysis. Time to first event, time to death or time until the censoring date of 16/05/2013 (if still alive with no events) was calculated.

Covariates

To allow adjustment for potential confounders, a series of covariates were identified. These were chosen by assessing their possible effects on hip fracture risk, co morbidity and possible interaction with Allopurinol therapy. Details of age and sex were acquired from population records contained within HIC data. Information regarding previous hospital admission with a

diagnosis of myocardial infarction, stroke, heart failure or chronic obstructive pulmonary disease were obtained from ICD-10 codes also contained within HIC database data. Diagnosis of diabetes mellitus was obtained from the SCI-DC dataset (19), which records all diagnoses of diabetes for Scotland. The most recent creatinine measurement prior to the date of social work assessment was obtained from routinely collected biochemistry records held in HIC.

Bisphosphonate medication and calcium and vitamin D use at the time of social work assessment were included as covariates. HIC data records dispensed community (not in-hospital) prescriptions for all participants; use of medications was flagged as positive if at least one dispensed prescription was recorded within three months of the index date. We extracted data on whether a package of social care (defined as any frequency of home visits for personal care paid for by the Social Work service) was in place within a month of social work assessment; this indicator was used as a proxy measure of functional impairment given that direct measures of impairment in physical or social function are not held as part of routinely collected electronic data in the study area.

Data Analysis

All data analyses were performed using STATA v14 (STATA Corp, New York, USA). A p value of <0.05 was taken as significant for all analyses. We used Fine and Gray competing risks models to estimate the effect of cumulative allopurinol exposure (as a time-dependant variable) on time to first hip fracture, with death as a competing risk. We used time-dependent Cox-regression analysis to model the effect of allopurinol on time to death. Unadjusted analyses were performed, along with analyses including the following covariates: age, sex, creatinine, albumin, haemoglobin, diagnosis of diabetes mellitus, previous admission with ischaemic heart disease, stroke, chronic heart failure, COPD, bisphosphonate prescription, vitamin D and calcium prescription, any exposure to allopurinol prior to the index date, and

provision of a package of social care. We performed sensitivity analysis using multiple imputation to account for missing baseline covariates, and a further sensitivity analysis including only those patients with exposure to allopurinol at any time; this was done as an alternative to propensity score matching as baseline predictors were unable to accurately calculate propensity for allopurinol use. For each analysis, cumulative exposure to allopurinol post-discharge was included as the time-dependent covariate, taking into account that doses varied from 100mg per day to 300mg per day. Cumulative exposure was expressed as equivalent years of 300mg exposure (thus a year of exposure to 100mg per day of allopurinol would count as one third of a year exposure). We also analysed time to first hip fracture separately for males and females, given the very different event rates seen in these populations.

Results

17308 patients who were alive without a prior hip fracture at the time of social work assessment were included in the study cohort. The mean follow up time was 7.2 (SD 4.4) years. Baseline details of the cohort are given in Table 1. 1401 (8.1%) of patients had missing covariates (haemoglobin or creatinine) and were thus not included in the Cox regression analyses, leaving a total of 15907 patients included in the final analysis. Of these, 565 were admitted to hospital with hip fracture.

Table 2 shows the results of the regression analyses for each outcome. We also performed subgroup analyses for males and females separately; the hazard ratio for hip fracture per year of allopurinol exposure was 1.03 (95% CI 1.01 to 1.04; p<0.001) for females, and 1.01 (95% CI 0.99 to 1.03; p=0.28) for males, but with no significant interaction on formal interaction testing.

Sensitivity analyses showed little difference; when including only those patients with any exposure at any time to allopurinol, the risk of hip fracture per year of exposure post-assessment was 1.00 (95%CI 0.99 to 1.02; p=0.62) and for death was 1.00 (95%CI 0.99 to 1.00; p=0.18). No difference in effect sizes was noted using multiple imputation to account for missing haemoglobin and creatinine data.

Discussion

This analysis is the first to our knowledge to examine the relationship between allopurinol use and hospitalisation for hip fracture. A key feature of the analysis was our ability to adjust for a range of important potential modifiers of risk, including functional status, as well as the use of routinely collected outcome and community prescribing data. Despite these adjustments, neither cumulative nor previous exposure to allopurinol was associated with differences in rates of death or hip fracture.

Previous studies have found a variable relationship between serum urate and osteoporosis and fractures. Several studies found that higher serum urate (which is a major risk factor for gout) is associated with higher bone mineral density and a lower risk of fracture [10-14]; one recent study showed no relationship between serum urate and fracture rates in older people [21], another recent study found that higher urate was associated with higher fracture rates in men [22]. Gout, ascertained by any use of allopurinol in a large Danish registry, was associated with higher fracture rates in men but not women [23]. Although urate has been postulated to have protective effects on bone loss via antioxidant effects, such effects might be lost or overwhelmed by the inflammatory stimulus of gout; inflammation is thought to drive both osteoporosis and sarcopenia, which could explain the divergent associations seen between fracture risk and gout and asymptomatic hyperuricaemia and fracture risk. In addition, uric acid

has been shown to suppress 1-alpha hydroxylase activity, accounting for associations found between high urate and high PTH, and between high urate and lower serum 1,25 hydroxyvitamin D [24]; these changes would again be expected to have deleterious effects on bone health.

Allopurinol use has been associated with improved functional outcomes after rehabilitation in older people [15], and recent *in vitro* work has shown that allopurinol and its active metabolite, oxypurinol, both enhance bone formation by osteoblasts in culture [25]. It is therefore possible that whilst allopurinol provides some potential beneficial effects on bone metabolism and muscle function, its actions in reducing urate levels (which themselves have antioxidant activity) negates these by removing the beneficial effects of urate on bone health. Thus the two effects would cancel out, showing no net effect on hip fracture rates as we observed. Other explanations are possible, particularly due to confounding. For instance the presence of heart failure is a powerful risk factor for both death and fractures. Treatment of heart failure entails use of diuretics – which may increase the risk of symptomatic gout and hence allopurinol prescription. Thus allopurinol use would be greater in the group of patients at higher risk of death or fracture – hence masking any potential beneficial effect of allopurinol.

Our study had a number of strengths. Use of routinely collected data greatly improves the generalizability of our results; such data includes patients with cognitive impairment and frailty that would usually preclude entry to clinical trials or cohort research studies. Using social work data allows the presence of a package of social care (as a proxy measure of physical function) to be used as a covariate – critical in studies of falls and fracture risk, yet often not obtainable from routinely collected healthcare data. We were also able to use data on dispensed prescriptions, which gives a robust estimate of cumulative drug exposure, and allows for

adjustment for other prescriptions known to influence fracture risk. The high death rate in this cohort poses the issue of competing risks, but the use of Fine and Gray modelling takes this issue into account. Finally, the use of multiple indices of allopurinol exposure, including a factor to characterise ever-exposure to allopurinol, allows for at least some minimisation of confounding by indication.

A number of weaknesses deserve comment. Only a small proportion of patients were exposed to allopurinol, limiting the power of the study. We limited our analysis to hip fracture, as this invariably leads to hospitalisation. Other fractures (e.g. of wrist or pelvis) do not always lead to hospitalisation, and thus the use of hospital data such as in this study cannot ascertain all occurrences of such fractures. Routinely collected data may suffer from incomplete ascertainment and inaccurate coding, which are further potential sources of bias if they affect the exposure groups differentially. We did not have access to a direct measure of physical or psychosocial function, as such measures are not collected electronically on all older people in the study area; the presence of a package of social care provides an indirect measure of functional impairment, but the need for such a package is moderated by other variables, such as the environment the patients lives in, and the amount of informal care (e.g. from spouse or offspring) available to the patient.

Despite access to a range of covariates associated with falls and fracture risk, there are a number of variables that we were unable to adjust for. We do not have access to data on bone mineral density, body mass index, cognitive function or balance – all important variables in ascertaining fracture risk. Higher body mass index in particular is associated with lower risk of fracture, but is also linked to higher urate levels and hence indications for use of allopurinol. Functional status was ascertained at a single point in time, and we are therefore unable to account for

changes in functional status and falls risk over time; the measure we used was a proxy for functional impairment, and direct measurements of lower limb function and balance would provide more accurate data on fall and fracture risk.

Lastly, and most importantly, any observational analysis cannot completely account for confounding by indication. This is a particular problem for studies of allopurinol – the drug is given only for gout, and gout is closely associated with elevated urate levels. Elevated urate is in turn a powerful marker of vascular disease and death [26], and vascular disease is in turn associated both with osteoporosis and with functional impairment [27]. In our analysis, allopurinol use was much more common in those with a previous hospital admission for myocardial infarction or heart failure. This may be driven by diuretic use in these conditions, which is known to precipitate gout and would therefore be expected to lead to greater use of allopurinol. Only randomised controlled trials will be able to dissect out whether allopurinol use might be causally linked to differences in death rates and fractures, but in the meantime, future observational work using larger databases with more events would help to ascertain whether there is a statistically and clinically significant association between allopurinol use, falls and fragility fractures.

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Table 1. Baseline details

	Ever exposed to allopurinol (n=1115)	Not exposed to allopurinol (n=16153)	p
Mean age (years) (SD)	73.2 (8.4)	73.4 (9.0)	0.44
Female sex (%)	487 (43.7)	9684 (60.0)	<0.001
Previous admission with myocardial infarction (%)	175 (15.7)	1269 (7.9)	<0.001
Previous admission with stroke (%)	64 (5.7)	973 (6.0)	0.50
Previous admission for heart failure (%)	175 (15.7)	782 (4.8)	<0.001
Previous admission for chronic obstructive pulmonary disease (%)	85 (7.6)	1046 (6.5)	0.24
Diabetes mellitus (%)	268 (24.0)	1972 (12.2)	<0.001
Baseline creatinine (umol/L) (SD)	131 (105)	94 (54)	<0.001
Baseline haemoglobin (g/dL) (SD)	12.5 (2.1)	12.8 (1.9)	<0.001
Baseline use of calcium+vitamin D (%)	69 (6.2)	8998 (5.6)	0.56
Baseline use of bisphosphonates (%)	40 (3.6)	698 (4.3)	0.16
Admission for hip fracture (%)	25 (2.2)	593 (3.7)	0.008
Died during follow up (%)	362 (32.5)	3864 (23.9)	<0.001
Receiving care package at baseline (%)	68 (6.1)	1119 (6.9)	0.18

Table 2. Time-dependent Cox regression analysis – time to hip fracture and death

	Hip fracture		Death	
Factor	HR (95% CI)	p	HR (95% CI)	p
Unadjusted analysis				
Allopurinol exposure (per year)	1.01 (0.99-1.02)	0.34	1.00 (1.00-1.01)	0.56
*Adjusted analysis**				
Allopurinol exposure (per year)	1.01 (0.99-1.02)	0.37	1.00 (0.99-1.01)	0.47
Age	1.06 (1.05-1.07)	<0.001	1.02 (1.02-1.03)	<0.001
Sex (female)	1.95 (1.60-2.37)	<0.001	0.60 (0.56-0.64)	<0.001
Myocardial infarction	1.01 (0.74-1.37)	0.96	1.10 (1.00-1.22)	0.05
Stroke	1.40 (1.05-1.88)	0.02	1.32 (1.17-1.48)	<0.001
Heart failure	1.09 (0.77-1.53)	0.63	1.81 (1.63-2.00)	<0.001
Chronic obstructive pulmonary disease	1.18 (0.84-1.65)	0.34	2.05 (1.87-2.26)	<0.001
Diabetes mellitus	0.90 (0.68-1.18)	0.43	1.07 (0.98-1.17)	0.11
Creatinine (per umol/L)	1.001 (1.000-1.002)	0.16	1.001 (1.001-1.001)	<0.001
Haemoglobin (per g/dL)	0.99 (0.94-1.04)	0.70	0.80 (0.79-0.81)	<0.001
Previous allopurinol use	0.76 (0.45-1.26)	0.28	1.13 (0.99-1.29)	0.07
Bisphosphonate use	1.75 (1.19-2.59)	0.004	1.02 (0.85-1.24)	0.81

Calcium/vitamin D use	1.43 (0.97-2.11)	0.07	0.83 (0.70-0.98)	0.03
Package of care	2.59 (1.97-3.41)	<0.001	0.30 (0.24-0.37)	<0.001

*Forced entry multivariable model; each variable adjusted for others in the model.